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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/049,865	03/27/1998	COLLIN J. WEBER	47765/C/JPW/	6162

7590 06/24/2004

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EXAMINER	
DAVIS, MINH TAM B	
ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 06/24/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/049,865	WEBER ET AL.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *54-59 and 62-70* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *54-59, 62-70* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on **04/15/04** has been entered.

Accordingly, claims 54-59, 62-70 are being examined.

The following are the remaining rejections.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, SCOPE

Rejection under 35 USC 112, first paragraph, of claims 54-59, 62-69 pertaining to while being enabled for a method for transplanting a viable xenogeneic cell or tissue, using CTLA4 or CTLA4Ig and microencapsulation of the cell or tissue, but not enabled for a method for transplanting a viable xenogeneic cell or tissue, using "an agent" that inhibits an immune system costimulation event and microencapsulation of the cell or tissue, remains for reasons already of record in paper of 03/17/2004.

Applicant argues that the rejection should not apply to claim 70 because claim 70 does not recite an "agent".

Applicant further argues that although the Examiner does not object to applicants' assertion that the range of possible inhibitors is limited to those which inhibit the interaction of the B7 receptor with the CTLAM receptor, nevertheless, the Examiner maintains the rejection the grounds that this "range of possible inhibitors is not limited, (encompasses) a whole universe of inhibitors, and applicant has not taught how to make these molecules use the claimed method." Applicant asserts that thus, the Examiner concedes that are there are art-recognized inhibitors be used claimed methods, however, the Examiner requires applicants' specification teach how to make **all** (emphasis added) possible inhibitors of B7:CTLAM receptor interaction in order to enable the claimed methods. Applicants maintain that the Examiner lacks any basis for imposing such a requirement.

Applicant asserts that the Examiner does not dispute that the specification discloses at least one method of making and using the claimed invention which correlates with the entire scope of the claim. Applicant asserts that as long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied." M.P.E.P. 12164.01(b).

Applicant's arguments set forth in paper of 04/15/04 have been considered but are not deemed to be persuasive for the following reasons:

By typographic error, Claim 70 was inadvertently included in the rejection of prior Office action. Claim 70 has been withdrawn from this instant 112, first paragraph rejection. The Examiner apologizes for any inconvenience incurred.

The Examiner takes note that the definition of inhibitors of an immune system costimulation event mediated by a cell surface molecule, such as B7 on the APC, or CD28 or CTLA4 on the T-cells is not limiting to B7 monoclonal antibodies, CTLA4Ig, CD28Ig or B7Ig, but includes numerous inhibitors with diverse structure, such as small molecule inhibitors or mimetics of B7 or CTLA4, or CD28, in additions to small molecule inhibitors or mimetics of analogs of B7 or CTLA4, or CD28, as defined in the specification, wherein the structure of the small molecule inhibitors or mimetics and the analogs of B7 or CTLA4, or CD28 is not disclosed in the specification.

Contrary to Applicant assertion, the Examiner did not and does not require that Applicant discloses how to make all of these inhibitors. Due to the lack of disclosure of any common structure for these inhibitors in the claimed method, or any information about the binding site on B7 or CTLA4 and its conformation where the small molecule inhibitors or mimetics would bind, one would not know how to make a representative number of species of inhibitors as claimed. The structure of these small molecule inhibitors or mimetics however are unpredictable, such that it would be undue experimentation for screening these inhibitors.

Further, contrary to Applicant assertion, the Examiner did not and does not agree that the specification discloses at least one method of making and using the claimed invention which correlates with the entire scope of the claim. As a matter of fact, the rejection is based on the lack of correlation between an example using a single inhibitor that interacts with CTLA4, CTLAIg, with the scope of the claimed method, in view that

the structure of the inhibitors in the claimed method is diverse and not predictable, and one does not know how to make the inhibitors in the claimed method.

It is noted that MPEP 2164.03 teaches that "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature ot the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to explicitly stated in the specification. In constrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order to be enabling."

Given the unpredictability of the structure of the inhibitors used in the claimed method, the lack of adequate disclosure in the specification, and in view of the complex nature of the claimed invention, and little is known in the art about the claimed invention, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

REJECTION UNDER 35 USC 103

Claims 54-59, 62-70 remain rejected under 35 USC 103, pertaining to obviousness over Lenschow et al, in view of Goosen et al, Soon-Shiong et al, Akalin et

al, Linsley et al, Padrid et al, and Steurer et al for reasons already of record in paper of 03/17/04.

Applicant asserts that the Examiner has failed to demonstrate either a suggestion in the prior art to combine microencapsulation with an inhibitor the B7:CTLA4 receptor interaction, or a reasonable expectation that this combination would improve the survival of microencapsulated grafts.

Applicant asserts that the Examiner's formulation of the relevant art that graft rejection due to infiltration of lymphocytes (Lenschow) and microencapsulation preventing graft rejection by protecting from both cytotoxic lymphocytes and natural killer cells and immune system proteins (Soon-shiong and Goosen) would make CTLA4Ig treatment redundant, and not complementary, in view that CTLA4Ig blocks a specific interaction between an APC and host T-cell that is required for full T-cell activation (see Padrid, 1998, of record).

Applicant asserts that Lenshow teaches away from the claimed invention Applicant asserts that Lenshow teaches that the immune response to *human* islets involves *human* APCs, and that CTLA4Ig prolongs graft survival by inhibiting interaction between *mouse* T cells which infiltrate the graft and *human* APCs which present the graft antigens (emphasis added). Applicant asserts that the Examiner acknowledges that such a cell:cell interaction would be blocked by microencapsulation of the graft. Applicant asserts that Lenshow teaches that this possibility contrasts with conclusions drawn in previous studies that predominant pathway for xenogeneic antigen presentation appears to involve the processing and presentation of shed foreign

proteins by syngeneic mouse APCs. Applicant asserts that the prevailing view is that this process by mouse APCs presenting shed foreign proteins are the primary means of stimulating the mouse T-cell response, and that the Examiner acknowledges the expectation that this process would also be blocked by microencapsulation, since the capsule was impermeable to immune system proteins as well as to cells. Applicant concludes that thus the art provides no reasonable expectation that combining CTLA4Ig treatment with encapsulation would improve graft survival over encapsulation alone.

Applicant asserts that none of the secondary references, when combined with Lenshow, Soo-Shiong and Goosen overcome this deficiency of motive and expectation of success in combining CTLA4Ig with microencapsulation to enhance graft survival.

Applicant asserts that in even a 1992 Soon-Shiong reference, two years after the Soon-Shiong reference cited by the Examiner, teaches away from the claimed invention. Applicant asserts that Soon-Shiong, 1992, despite discussing a number of areas for further research, does not suggest combining microencapsulation with inhibition of the B7:CTLA4 receptor interaction. Applicant asserts that instead, Soon-shiong suggests other, entirely different avenues of research, specifically optimization of cyclosporin dosages to inhibit the cytokines IL-I and TNF (see pg. 769, 773) and improvements in microcapsule design (p. 769, 773). Thus, Applicant maintains that the prior art teaches away from the claimed invention.

Applicant's arguments set forth in paper of 04/15/04 have been considered but are not deemed to be persuasive for the following reasons:

Contrary to Applicant's arguments, Lenshow et al do not teach away from the claimed invention. It is noted that Lenschow et al teach that transient immunosuppression can lead to permanent islet graft acceptance because of graft adaptation (the loss of immunogenecity as a result of the loss of APC function) (p.791, third column, second paragraph). Lenschow et al further teaches that CTLA4Ig, by directly preventing T cell recognition of the B7 antigen-presenting cells (APCs), prolongs donor specific unresponsiveness to islet graft (figure 4, and p.791, third column, last two paragraphs bridging p.792). It is further noted that although microencapsulation of the islets could prevent the penetration of host immune cells, such as natural killer cells and cytotoxic T lymphocytes, and macrophages (Soon-Shiong at p.218), and the penetration of large damaging molecules that are produced by immune cells (Goosen et al), however, different from CTLA4Ig, microcapsules cannot prevent the interaction of donor specific APCs and T cells outsides of the grafts, wherein preventing such interaction of APCs can lead to loss of APCs function, and consequently graft adaptation and prolonging graft acceptance, as taught by Lenschow et al. In addition, different from encapsulation, CTLA4Ig cannot prevent penetration of large damaging molecules that are produced by host immune cells.

Thus one would have expected that treatment by CTLA4Ig would complement encapsulation, because by directly preventing T cell recognition of the B7 antigen-presenting cells, CTLA4Ig not only reduces activation of T cells, thus reducing the number of host immune cells, but also induces long term donor-specific tolerance, which would be useful in organ transplantation, as taught by Lenschow et al. One would

have been motivated to combine the teaching of Lenschow with Soon-Shiong and Goosen with a reasonable of expectation of success, because CTLA4Ig treatment as taught by Lenschow et al, and encapsulation of islets taught by Soon-Shiong and Goosen are complementary to each other, i.e. reducing damaging by host immune cells to islets by different mechanisms, in addition to additional beneficial effect of long term donor-specific tolerance by CTLA4Ig alone, and prevention of penetration of large damaging molecules by encapsulation alone, and thus a combination of both treatment would enhance the chance of enhancing graft survival.

Moreover, contrary to Applicant's assertion, Soon-Shiong, 1992 do not teach away from the claimed invention. It is noted that the reference by Soon-Shiong, 1992, teaches how to improve encapsulation, by optimization of cyclosporin dosages to inhibit the damaging cytokines IL-I and TNF, which are induced by a chemical component of the encapsule membrane, mannuronic acid (Soon-Shiong, 1992, p.769, second column, second paragraph). Thus whether or not Soon-Shiong, 1992, suggests how to improve prevention of graft rejection in general is not germane.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 9:30AM-4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, CHRISTINA CHAN can be reached on 571-272-0841. The fax phone

number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

MINH TAM DAVIS

June 18, 2004

SUSAN UNGAR, PH.D
PRIMARY EXAMINER